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(54) Substituted benzo(b)thiophene compounds having activity as selective estrogen receptor modulators

Substituierte Benzo(b)thiophene als selektive Östrogenrezeptormodulatoren

Benzothiophènes substitués actifs comme modulateurs du récepteur oestrogénique

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The file contains technical information submitted after the application was filed and not included in this specification

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Description

[0001] This invention relates to organic compounds having pharmacological activity, to compositions containing the compounds, to medical methods of treatment employing the compounds, and to chemical processes and intermediates for their production. More particularly, the present invention concerns a class of (substituted alkylaminophenyl)- and (substituted alkylthiophenyl)benzo[*b*]thiophene compounds, pharmaceutical formulations containing the compounds, their use in the treatment of conditions associated with post-menopausal syndrome, and estrogen dependent cancers, uterine fibroid disease, endometriosis, and aortal smooth muscle cell proliferation.

[0002] "Post-menopausal syndrome" is a term used to describe various pathological conditions which frequently affect women who have entered into or completed the physiological metamorphosis known as menopause. Although numerous pathologies are contemplated by the use of this term, three major effects of post-menopausal syndrome are the source of the greatest long-term medical concern: osteoporosis, cardiovascular effects such as hyperlipidemia, and estrogen-dependent cancer, particularly breast and uterine cancer.

[0003] Osteoporosis describes a group of diseases which arise from diverse etiologies, but which are characterized by the net loss of bone mass per unit volume. The consequence of this loss of bone mass is the failure of the skeleton to provide adequate structural support for the body resulting in bone fractures.

[0004] One of the most common types of osteoporosis is that associated with menopause. Most women lose from about 20% to about 60% of the bone mass in the trabecular compartment of the bone within 3 to 6 years after the cessation of mensus. This rapid loss is generally associated with an increase of bone resorption and formation. However, the resorptive cycle is more dominant and the result is a net loss of bone mass. Osteoporosis is a common and serious disease among post-menopausal women.

[0005] There are an estimated 25 million women in the United States, alone, who are afflicted with this disease. The results of osteoporosis are personally harmful and also account for a large economic loss due to its chronicity and the need for extensive and long term support (hospitalization and nursing home care) from the disease sequelae. This is especially true in more elderly patients. Additionally, although osteoporosis is not generally thought of as a life threatening condition, a 20% to 30% mortality rate is related with hip fractures in elderly women. A large percentage of this mortality rate can be directly associated with post-menopausal osteoporosis.

[0006] The most vulnerable tissue in the bone to the effects of post-menopausal osteoporosis is the trabecular bone. This tissue is often referred to as spongy or cancellous bone and is particularly concentrated near the ends of the bone (near the joints) and in the vertebrae of the spine. The trabecular tissue is characterized by small osteoid structures which inter-connect with each other, as well as the more solid and dense cortical tissue which makes up the outer surface and central shaft of the bone. This interconnected network of trabeculae gives lateral support to the outer cortical structure and is critical to the biomechanical strength of the overall structure.

[0007] In post-menopausal osteoporosis, it is primarily the net resorption and loss of the trabeculae which leads to the failure and fracture of bone. In light of the loss of the trabeculae in post-menopausal women, it is not surprising that the most common fractures are those associated with bones which are highly dependent on trabecular support, e.g., the vertebrae, the neck of the weight bearing bones such as the femur and the fore-arm. Indeed, hip fracture, collies fractures, and vertebral crush fractures are hall-marks of post-menopausal osteoporosis.

[0008] At this time, the only generally accepted method for treatment of post-menopausal syndrome is estrogen replacement therapy. Although therapy is generally successful, patient compliance with the therapy is low primarily because estrogen treatment frequently produces undesirable side effects.

[0009] Prior to menopause, most women have less incidence of cardiovascular disease than age-matched men. Following menopause, however, the rate of cardiovascular disease in women increases to match the rate seen in men. This increased risk has been linked to the loss of estrogen and, in particular, to the loss of estrogen's ability to regulate the levels of serum lipids. The nature of estrogen's ability to regulate serum lipids is not well understood, but evidence to date indicates that estrogen can upregulate the low density lipid (LDL) receptors in the liver to remove excess cholesterol. Additionally, estrogen appears to have some effect on the biosynthesis of cholesterol, and other beneficial effects on cardiovascular health.

[0010] It has been reported in the literature that post-menopausal women undergoing estrogen replacement therapy experience a return of serum lipid concentrations to those of the pre-menopausal state. Thus, estrogen would appear to be a reasonable treatment for this condition. However, the side-effects of estrogen replacement therapy are not acceptable to many women, thus limiting the use of this therapy. An ideal therapy for this condition would be an agent which would regulate the serum lipid levels as does estrogen, but would be devoid of the side-effects and risks associated with estrogen therapy.

[0011] The third major pathology associated with post-menopausal syndrome is estrogen-dependent breast cancer and, to a lesser extent, estrogen-dependent cancers of other organs, particularly the uterus. Although such neoplasms are not solely limited to a post-menopausal women, they are more prevalent in the older, post-menopausal population. Current chemotherapy of these cancers has relied heavily on the use of anti-estrogen compounds such as, for example,

Tamoxifen. Although such mixed agonist-antagonists have beneficial effects in the treatment of these cancers, and the estrogenic side-effects are tolerable in acute life-threatening situations, they are not ideal. For example, these agents may have stimulatory effects on certain cancer cell populations in the uterus due to their estrogenic (agonist) properties and they may, therefore, be contraproductive in some cases. A better therapy for the treatment of these cancers would be an agent which is an anti-estrogen compound having negligible or no estrogen agonist properties on reproductive tissues.

[0012] In response to the clear need for new pharmaceutical agents which are capable of alleviating the symptoms of, *inter alia,* post-menopausal syndrome, the present invention provides new compounds, pharmaceutical compositions thereof, and methods of using such compounds for the treatment of post-menopausal syndrome and other estrogen-related pathological conditions such as those mentioned below. The reduction of bone density and mass leading to osteoporosis that more rarely occurs in men is also tied to the loss of hormonal regulation and is, therefore, also a target for therapy according to the compounds and methods of the current invention.

[0013] Uterine fibrosis is an old and ever present clinical problem known by a variety of names, including uterine hypertrophy, uterine lieomyomata, myometrial hypertrophy, fibrosis uteri, and fibrotic metritis. Essentially, uterine fibrosis is a condition where there is an inappropriate deposition of fibroid tissue on the wall of the uterus.

[0014] This condition is a cause of dysmenorrhea and infertility in women. The exact cause of this condition is poorly understood but evidence suggests that it is an inappropriate response of fibroid tissue to estrogen. Such a condition has been produced in rabbits by daily administrations of estrogen for 3 months. In guinea pigs, the condition has been produced by daily administration of estrogen for four months. Further, in rats, estrogen causes similar hypertrophy.

[0015] The most common treatment of uterine fibrosis involves surgical procedures both costly and sometimes a source of complications such as the formation of abdominal adhesions and infections. In some patients, initial surgery is only a temporary treatment and the fibroids regrow. In those cases a hysterectomy is performed which effectively ends the fibroids but also the reproductive life of the patient. Also, gonadotropin releasing hormone antagonists may be administered, yet their use is tempered by the fact they can lead to osteoporosis.

[0016] Endometriosis is a condition of severe dysmenorrhea, which is accompanied by-severe pain, bleeding into the endometrial masses or peritoneal cavity and often leads to infertility. The cause of the symptoms of this condition appear to be ectopic endometrial growths which respond inappropriately to normal hormonal control and are located in inappropriate tissues. Because of the inappropriate locations for endometrial growth, the tissue seems to initiate local inflammatory-like responses causing macrophage infiltration and a cascade of events leading to initiation of the painful response. The exact etiology of this disease is not well understood and its treatment by hormonal therapy is diverse, poorly defined, and marked by numerous unwanted and perhaps dangerous side effects.

[0017] One of the treatments for this disease is the use of low dose estrogen to suppress endometrial growth through a negative feedback effect on central gonadotropin release and subsequent ovarian production of estrogen; however, it is sometimes necessary to use continuous estrogen to control the symptoms. This use of estrogen can often lead to undersirable side effects and even the risk of endometrial cancer.

[0018] Another treatment consists of continuous administration of progestins which induces amenorrhea and by suppressing ovarian estrogen production can cause regressions of the endometrial growths. The use of chronic progestin therapy is often accompanied by the unpleasant CNS side effects of progestins and often leads to infertility due to suppression of ovarian function.

[0019] A third treatment consists of the administration of weak androgens, which are effective in controlling the endometriosis; however, they induce severe masculinizing effects. Several of these treatments for endometriosis have also been implicated in causing a mild degree of bone loss with continued therapy. Therefore, new methods of treating endometriosis are desirable.

[0020] Aortal smooth muscle cell proliferation plays an important role in diseases such as atherosclerosis and restenosis. Vascular restenosis after PTCA has been shown to be a tissue response characterized by an early and late phase. The early phase occuring hours to days after PTCA is due to thrombosis with some vasospasms while the late phase appears to be dominated by excessive proliferation and migration of aortal smooth muscle cells. In this disease, the increased cell motility and colonization by such muscle cells and macrophages contribute significantly to the pathogenesis of the disease. The excessive proliferation and migration of vascular aortal smooth muscle cells may be the primary mechanism to the reocclusion of coronary arteries following PTCA, atherectomy, laser angioplasty and arterial bypass graft surgery. See "Intimal Proliferation of Smooth Muscle Cells as an Explanation for Recurrent Coronary Artery Stenosis after Percutaneous Transluminal Coronary Angioplasty," Austin *et al., Journal of the American College of Cardiology 8*: 369-375 (Aug. 1985).

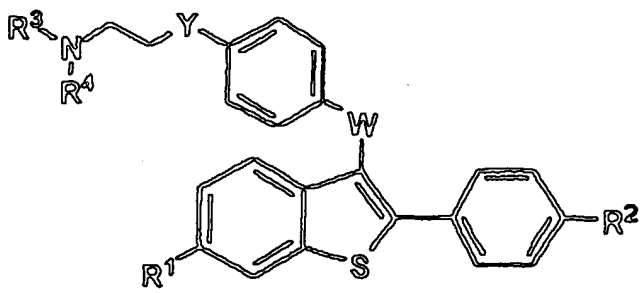
[0021] Vascular restenosis remains a major long term complication following surgical intervention of blocked arteries by percutaneous transluminal coronary angioplasty (PTCA), atherectomy, laser angioplasty and arterial bypass graft surgery. In about 35% of the patients who undergo PTCA, reocclusion occurs within three to six months after the procedure. The current strategies for treating vascular restenosis include mechanical intervention by devices such as stents or pharmacologic therapies including heparin, low molecular weight heparin, coumarin, aspirin, fish oil, calcium

antagonist, steroids, and prostacyclin. These strategies have failed to curb the reocclusion rate and have been ineffective for the treatment and prevention of vascular restenosis. See "Prevention of Restenosis after Percutaneous Transluminal Coronary Angioplasty: The Search for a 'Magic Bullet'", Hermans *et al., American Heart Journal 122*: 171-187 (July 1991).

[0022] In the pathogenesis of restenosis, excessive cell proliferation and migration occurs as a result of growth factors produced by cellular constituents in the blood and the damaged arterial vessel wall, which factors mediate the proliferation of smooth muscle cells in vascular restenosis.

[0023] Agents that inhibit the proliferation and/or migration of aortal smooth muscle cells are useful in the treatment and prevention of restenosis. The present invention provides for the use of compounds as aortal smooth muscle cell proliferation inhibitors and, thus, inhibitors of restenosis.

[0024] In its principal embodiment, the present invention provides a compound having the formula:



or a pharmaceutically acceptable salt thereof wherein $\mathbf{R^1}$ and $\mathbf{R^2}$ are independently selected from the group consisting of hydroxy and -O(C_1-C_6 alkyl).

[0025] The linking group **W** is CHOH, C(O), or CH_2; and **Y** is -S-.

[0026] The substituents $\mathbf{R^3}$ and $\mathbf{R^4}$ together with the nitrogen to which they are attached combine to form a 1-pyrrolidinyl, 1-piperidinyl, or a 5- or 6-membered imide or cyclic amide ring.

[0027] In a second embodiment, the present invention provides pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I, optionally further comprising estrogen or progestin, in combination with a pharmaceutically acceptable carrier.

[0028] In yet another embodiment, the present invention comprises a method of treating osteoporosis, aortal smooth muscle cell proliferation, particularly restenosis, and estrogen-dependent cancer, particularly breast cancer.

[0029] As used throughout this specification and the appended claims, the following terms have the indicated definitions.

[0030] The term "alkyl" refers to a monovalent radical derived by the removal of a single hydrogen atom from a straight or branched-chain saturated hydrocarbon. Alkyl groups include, for example, methyl, ethyl, propyl, isopropyl, butyl, n-butyl, pentyl, isopentyl, hexyl, isohexyl, and the like.

[0031] The term "estrogen" includes steroidal compounds having estrogenic activity such as, for example, 17β-estradiol, estrone, conjugated estrogen (e.g., Premarin®), equine estrogen, 17α-ethynyl estradiol, and the like.

[0032] "Progestin" denotes compounds having progestational activity such as, for example, progesterone, norethynodrel, norgestrel, megestrol acetate, norethindrone, and the like.

[0033] Preferred compounds of this invention include compounds of formula I wherein W is -C(O)- and Y is -S-.

[0034] Certain R^3 and R^4 groups also demonstrate preferable characteristics. For example, those compounds of formula I wherein R^3 and R^4 together with the nitrogen to which they are attached form 1-pyrrolidinyl or 1-piperidinyl are preferred. A further preferred subgroup of the preferred 1-pyrrolidinyl or 1-piperidinyl compounds include those compounds wherein R^1 and R^2 are -OH or -OCH_3.

[0035] Particularly preferred compounds of formula I include those having all of the aforementioned limitations, that is, compounds wherein W is C(O); Y is S; R^1 and R^2 are -OH or -OCH_3, particularly wherein R^1 and R^2 are the same as one another; and R^3 and R^4, together with the nitrogen to which they are attached form 1-pyrrolidinyl or 1-piperidinyl.

[0036] Although the free-base or acid forms of formula I compounds can be used in the methods of the present invention, it is preferred to prepare and use a pharmaceutically acceptable salt form. Thus, the compounds used in the methods of this invention form pharmaceutically acceptable acid or base addition salts with a wide variety of organic and inorganic acids and bases, and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric, and the like. Salts derived from organic acids,

such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, b-hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, terephthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzenesulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. Preferred salts are the hydrochloride and oxalate salts.

[0037] Typical bases used to form pharmaceutically acceptable addition salts would be inorganic bases, such as, sodium hydroxide, potassium hydroxide, alkali carbonates or bicarbonates, calcium carbonate, magnesium carbonate, and the like. Additionally, organic bases may be utilized to form addition salts, e.g., alkyl amines, such as, triethylamine, dimethylamine, i-propylamine, and the like .

[0038] The pharmaceutically acceptable acid or base addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid or base. The reactants are generally combined in a mutual solvent such as diethyl ether or ethyl acetate. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

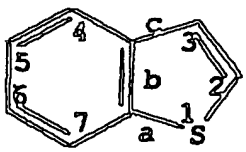
[0039] The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

[0040] Specific examples of compounds contemplated as falling within the scope of the present invention include, but are not limited to the following compounds and their pharmaceutically acceptable salts:

6-hydroxy-2-(4-hydroxyphenyl)-3-[(4-(2-(piperidin-1-yl)ethyl)thio)benzoyl]benzo[*b*]thiophene; and

6-methoxy-2-(4-methoxyphenyl)-3-[(4-(2-(piperidin-1-yl)ethyl)thio)benzoyl]benzo[*b*]thiophene.

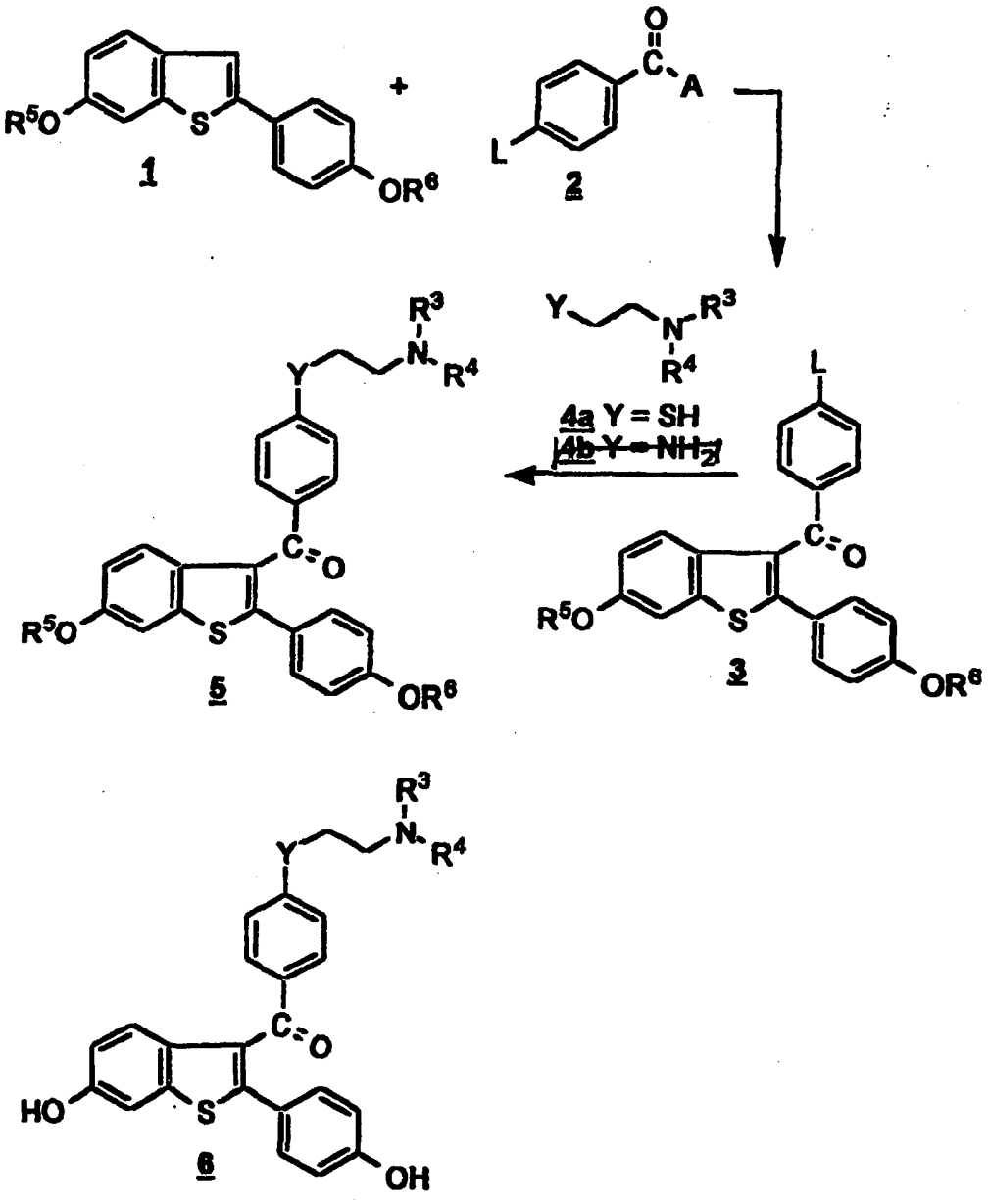
[0041] The compounds of the present invention are derivatives of benzo[b]thiophene which is named and numbered according to the Ring Index, The American Chemical Society, as follows:



and are synthesized by methods detailed in Reaction Schemes 1 and 2 below.

[0042] In the synthetic sequence for preparing compounds of the present invention depicted in Reaction Scheme 1, compounds of the present invention are synthesized by first reacting a protected 6-hydroxy-2-(4-hydroxyphenyl)benzo [b]thiophene, **1**, under Friedel-Crafts acylation conditions with an activated benzoyl derivative, **2**, which is substituted in the 4-position with a suitable leaving group, L.

Reaction Scheme 1



[0043] In compounds of formula 1, the protecting groups R^5 and R^6 are phenolic protecting groups capable of withstanding the conditions of the Friedel-Crafts acylation reaction and are of the type taught by T. Greene, *et al.* in Chapter 3 of "Protective Groups in Organic Synthesis," Second Edition, John Wiley & Sons, Inc., New York, 1991, pp.143-170. The preferred protecting groups are alkyl ether groups, with methyl being particularly preferred.

[0044] The leaving group, L, in compounds of formula 2 is selected from those groups known in the art to participate in nucleophilic aromatic substitution reactions (see J. March, "Advanced Organic Chemistry," 3rd Edition, John Wiley & Sons, New York, 1985, p. 587. Suitable leaving groups include fluoro, chloro, bromo, nitro, (lower alkyl)phenylsulfonyl, (lower alkyl)sulfonyl, phenylsulfonyl, azido, trialkylammonium, phenoxy, alkoxy, thioalkoxy, and amino.

[0045] For purposes of the present invention, the preferred leaving groups include fluoro, chloro, bromo, nitro, (lower alkyl)phenylsulfonyl, and lower alkylsulfonyl, with fluoro, bromo, and nitro being most preferred.

[0046] In compounds of formula 2, the activating group, A, is selected from groups well known in the art to activate acids for the purposes of carrying out Friedel-Crafts acylation reactions and include acid halides such as the fluoride,

chloride and bromide; mixed acid anhydrides with C_1-C_6 alkanoic acids, C_1-C_6 alkylsulfonic acids, arylsulfonic acids, C_1-C_6 alkylsulfonic acids, perfluorinated C_1-C_6 alkanoic acids, C_1-C_6 alkylcarbonates, arylcarbonates, and the like. The preferred compounds of formula **2** are those in which A is halogen, most preferably chlorine.

[0047] Typically, the acylation reaction betrween **1** and **2** is carried out in an inert organic solvent in the presence of a Lewis acid catalyst. Suitable solvents include halogentaed hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane, carbon tetrachloride, chlorobenzene, dichlorobenzene and the like. The amount of solvent is not critical, but is generally sufficient to enable efficient mixing of the reaction components.

[0048] Suitable Lewis acid catalysts for the Friedel-Crafts acylation reaction between **1** and **2** include anhydrous aluminum, boron, or zinc halides with aluminum chloride being preferred.

[0049] Temperature and time of reaction will vary, depending upon the choice of reaction solvent, Lewis acid catalyst, and activating group, A. Generally, reactions are carried out at temperatures below or at ambient to below or at the reflux temperature of the solvent. Reaction times vary from several minutes to about forty-eight hours. The progress of the reaction toward completion can be followed by well-known techniques such as thin-layer chromatographic analysis of aliquots of the reaction mixture during the course of the reaction.

[0050] Typically, the reaction is conducted using 1.0 to 1.5 equivalents of compound **2** for each equivalent of protected benzo[b]thiophene, **1**, with more of the activated benzoyl compound added during the course of the reaction as needed to drive the reaction to completion. The amount of Lewis acid catalyst employed ranges from between about 0.1 to 5 equivalents.

[0051] The product resulting from the acylation reaction, **3**, is reacted next with a compound of formula **4** in which R^3 and R^4 have the meanings ascribed to them above. In the case where Y is -SH in compounds of formula **4a**, the reaction between **3** and **4a** is carried out by mixing the two reagents in the presence of a strong base in a polar aprotic solvent. Suitable strong bases include alkyllithiums, alkali metal amides, or metal hydrodies such as lithium, potassium or sodium hydride, or lithium aluminum hydride or sodium aluminum hydride.

[0052] Suitable polar aprotic solvents include N,N-dimethylformamide, N-methyl pyrrolidinone, N,N'-dimethylpropylurea, dimethylsulfoxide, tetrahydrofuran, and the like.

[0053] Alternatively, the sulfhydryl compound, **4a**, can be separately converted to the corresponding anion by reaction with a strong base in a polar aprotic solvent, and the resulting anion subsequently reacted with compound **3**.

[0054] Following the acylation reaction between compounds **3** and **4**, the protecing groups of the resulting product, **5**, are removed by methods taught in the art to produce the dihydroxy compounds **6** (for deprotection reagents and reaction conditions,see T. Greene, *et al.* cited above and the references cited therein). In the case where R^5 and R^6 are the preferred protecting group, methyl, the deprotective removal of the methyl groups can be carried out either by the use of an alkali metal ethanethionate (see G. I. Fetruell, *et al.*, Tetrahedron Letters, 1327 (1970); *idem.* Aust. J. Chem., **25**: 1719 (1972) and A. S. Kende, *et al.*, Tetrahedron Letters, **22**: 1779 (1981) or by the use of either boron tribromide in methylene chloride at a temperature of between about -80_C to 20_C for a period of 6-12 hours (J. F. W. McOmie, *et al.*, Org. Syn., Coll. Volume V, 412 (1973)) or BBr_3-$S(CH_3)_2$ in ethylene chloride at a temperature of about 80_C to 85_C (P. G. Williard, *et al.*, Tetrahedron Letters, **21**: 3731 (1981)).

[0055] Compounds of the present invention in which W is CHOH are prepared following deprotection step by dissolution in an appropriate solvent and reaction with reducing agent, such as, for example, lithium aluminum hydride, under an inert gas such as nitrogen.

[0056] A compound of the present invention wherein W is CHOH are further reduced to provide compounds in which W is methylene via standard procedures. This is accomplished by suspending the compound in an appropriate solvent and cooling under an inert gas such as nitrogen. To this suspension is added a suitable trialkyl silane reducing agent, preferrably triethyl silyl, and a reasonably strong protic acid such as hydrochloric acid, trifluoroacetic acid, and the like.

[0057] Compounds of formula I can be prepared so that R^1 and R^2 are different biological protecting groups or, preferably, the same biological protecting group. Preferred protecting groups include -CH3, $-C(O)C(CH_3)_3$, $-C(O)C_6H_5$, and $-SO_2(CH_2)_3CH_3$.

[0058] In an alternative synthetic sequence illustrated in Reaction Scheme 2 below, compounds of the present invention where Y is -S- are prepared by first synthesizing the desired activated (4-substituted)benzoyl compound, **9**, (the acid chloride being illustrated). The intermediate is prepared by converting the 4-substituted benzoic acid compounds, **7** to their corresponding amine substituted derivatives, **8**. The substituted benzoic acids, **8** are converted to their corresponding acid chlorides, **9**, by conventional methods known in the art.

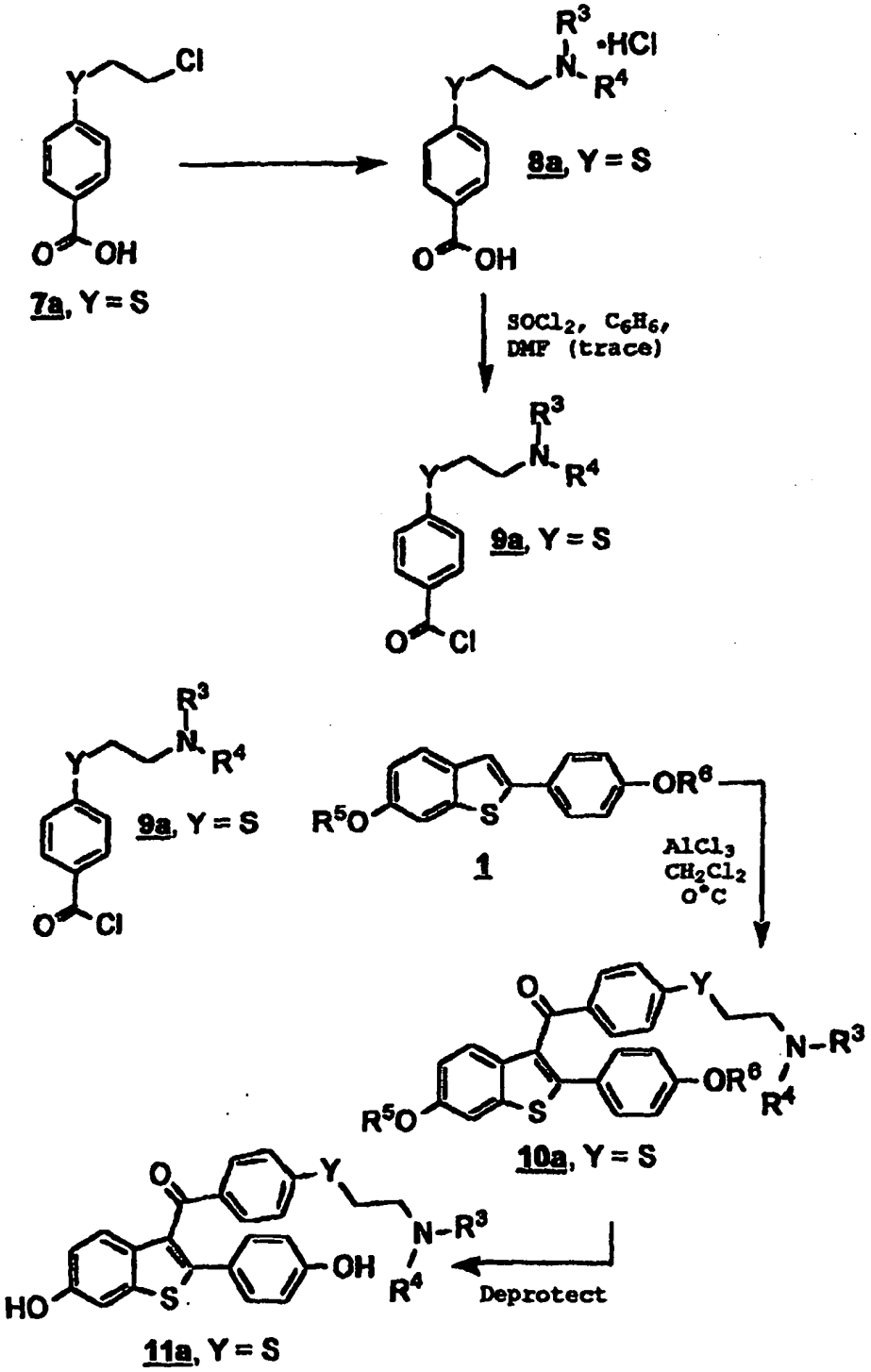
[0059] The acid chlorides, **9**, are reacted with a hydroxy-protected compound of formula **1** in a conventional Friedel-Crafts acylation reaction to produce the penultimate intermediates, **10**. Deprotection (removal of groups R^5 and R^6 produces the desired compounds of the present invention in which Y is -S-.

[0060] Compounds of formula I can be prepared so that R^1 and R^2 are different biological protecting groups or, preferably, the same biological protecting group. Preferred protecting groups include OCH_3, O-$C(O)$-$C(CH_3)_3$, O-$C(O)$-C_6H_5, and O-SO_2-$(CH_2)_3$-CH_3.

[0061] The term "biological protecting groups" refers to those R^1 and R^2 substituents which delay, resist, or prohibit

removal of such groups in a biological system such as, for example, following administration of a compound of the present invention containing the above-described R^1 and R^2 groups to a human. Such compounds also are useful for the methods herein described, especially when W is CH_2.

Reaction Scheme 2



[0062] All reagents obtained from commercial sources were used without further purification unless otherwise

indicated. ^1H and ^{13}C nuclear magnetic resonance spectra were measured as indicated at 300 and 75MHz respectively. ^1H-NMR chemical shifts are reported as δ values in ppm relative to the NMR solvent employed. ^1H-NMR coupling constants are reported in Hertz (Hz) and refer to apparent multiplicities, indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and b (broad), in conjuction with "s", "d", "t" etc. Column chromatography was performed according to the method of Still *et. al.* (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, 43:2923) unless otherwise indicated with EM Science silica gel (230-400 mesh ASTM). In all cases, concentrations were performed under reduced pressure with a rotary evaporator.

[0063] The following preparations and examples are presented as representative embodiments of the present invention and are not to be read as limiting the scope of the invention as it is defined by the appended claims.

Preparation of Intermediates

Preparation 1

Preparation of 6 -methoxy -2 - (4-methoxyphenyl)-3-(4-nitrobenzoyl)benzo[*b*]thiophene

[0064] To a slurry of 4-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (1.00 g, 3.70 mmol) in 25 mL of dichloroethane at 5_C was added 0.604 (4.52 mmol) of aluminum chloride. The slurry was observed to turn deep red. To this mixture was added 0.838 g (4.52 mmol) of 4-nitrobenzoyl chloride and the resulting mixture was stirred for one hour at 5_C and then for three hours at room temperature. Additional aluminum chloride (0.2932 g, 2.215 mmol) and 4-nitrobenzoyl chloride (0.4065 g, 2.19 mmol) were added, and the resulting mixture stirred for three hours.

[0065] A final charge of aluminum chloride (0.272 g, 2.06 mmol) was added, and the resuting mixture stirred at room temperature for sixteen hours. At the end of this time, the reaction was quenched by addition of cold 1N hydrochloric acid and the reaction mixture was partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was separated, washed sequentially with water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. The organic layer was collected, dried over anhydrous magnesium sulfate, filtered and concentrated to an oil which was then adsorbed on silica gel. Chromatography (2:1 hexanes:ethyl acetate) yielded 0.2744 g (18%) of the title compound as a solid, mp 168.9-170_C.

IR (KBr):	3140, 2820, 1659, 1603, 1528, 1347, 1251, 1045, 829 cm^{-1}.
^1H NMR ($CDCl_3$):	δ 8.04 (d, 2H, J = 8.9 Hz), 7.81 (m, 3H), 7.34 (d, 1H, J = 2.3 Hz), 7.21 (d, 1H, J = 8.7 Hz), 7.05 (dd, 1H, J = 8.7), 6.69 (d, 2H, J = 8.9 Hz), 3.91 (s, 3H), 3.71 (3H);
^{13}C NMR ($CDCl_3$):	δ 192.0, 160.3, 158.0, 149.7, 147.2, 142.7, 140.2, 133.3, 130.8, 130.6, 129.1, 125.4, 124.3, 123.3, 115.3, 114.1, 104.5, 55.7, 55.3;

Elemental Analysis:

Calc'd. for $C_{23}H_{17}NO_5S$: C, 65.86; H 4.08: N, 3.34; S, 7.64;
Found: C, 65.85; H, 4.11; N, 3.29; S, 7.51.

Preparation 2

Preparation of 6-methoxy-2-(4-methoxyphenyl)-3-(4-fluorobenzoyl)benzo[*b*]thiophene

[0066] To a slurry of 4-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (1.02 g, 3.77 mmol) in 25 mL of dichloroethane at 5_C was added 0.600 (4.5 mmol) of aluminum chloride. The slurry was observed to turn deep red. To this mixture was added 0.535 mL (0.718 g, 4.52 mmol) of 4-fluorobenzoyl chloride and the resulting mixture was stirred for twenty-four hours at 5_C and then quenched by addition of cold 20 mL of cold 1N hydrochloric acid. The reaction mixture was partitioned between dichloromethane and 1N hydrochloric acid. The organic layer was separated, and the aqueous layer was back extracted twice with dichloromethane. The organic layers were collected and washed saturated aqueous sodium chloride. The organic layer was collected, dried over anhydrous magnesium sulfate, filtered, concentrated and chromatographed on silica gel (8:1 hexanes:ethyl acetate) to yield 1.0879 g (74%) of the title compound as a solid, mp 108.1-109_C.

IR (KBr):	2980, 2940, 2810, 1640, 1598, 1473, 1251, 1152, 831 cm^{-1}.
^1H NMR ($CDCl_3$):	δ7.78 (dd, 2H, J = 5.6, 8.7 Hz), 7.61 (d, 1H, J = 8.9 Hz),7.28 (m, 3H), 6.98 (dd, 1H, J = 2.5, 8.9 Hz), 6.94 (m, 3H), 6.72 (d, 2H, J = 8.7 Hz), 3.88 (s, 3H), 3.73 (3H);
^{13}C NMR ($CDCl_3$):	δ 192.8, 167.4, 164.0, 160.0, 157.9, 144.3, 140.2, 134.0, 133.9, 133.8, 132.7, 132.5, 130.6, 130.0, 125.8, 124.2, 115.7, 115.5, 115.1, 114.1, 104.6, 55.7, 55.3;

^{19}F NMR ($CDCl_3$): δ 48.31 (t, J = 6 Hz);

Elemental Analysis:
Calc'd. for $C_{23}H_{17}FO_3S$: C, 70.39; H, 4.37; S, 8.17; F, 4.84;
Found: C, 70.21; H, 4.38;, S, 8.27; F, 5.14.

Preparation 3

Preparation of 6 -methoxy -2 - (4-methoxyphenyl) -3-(4-bromobenzoyl)benzo[*b*]thiophene

[0067] To a slurry of 4-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene (0.99 g, 3.66 mmol) in 25 mL of dichloroethane at 5_C was added 0.622 g (4.66 mmol) of aluminum chloride. The slurry was observed to turn deep red. To this mixture was added (0.997 g, 4.54 mmol) of 4-bromobenzoyl chloride and the resulting mixture was stirred for three hours at 5_C and then quenched by addition of cold 10 mL of cold 1N hydrochloric acid. The reaction mixture was partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was separated, and washed sequentially with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The organic layer was collected, dried over anhydrous magnesium sulfate, filtered, concentrated to an oil and chromatographed on silica gel (9:1 hexanes:ethyl acetate) to yield several fractions containing product. These fractions were combined, concentrated, and dried *in vacuo* at 100_C overnight to yield 1.0715 g (65%) of the title compound as a viscous oil.

IR ($CHCl_3$): 3030,1647, 1608, 1586, 1477, 1253, 831 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ 7.61 (m, 3H), 7.33 (m, 5H),6.98 (dd, 1H, J = 8.7, 2.1 Hz), 6.71 (d, 2H, J = 8.7 Hz), 3.83 (s, 3H), 3.69 (s, 3H), 3.69 (s, 3H);
^{13}C NMR ($CDCl_3$): δ 193.2, 160.1, 157.9, 144.7, 140.2, 136.4, 133.7, 131.7, 131.4, 130.6, 129.7, 128.3, 125.8, 124.2, 115.1, 114.2, 104.6, 55.7, 55.4;

[0068] A portion of the product material was recrystallized from ethyl acetate to obtain a sample for elemental analysis.
Elemental Analysis: Calc'd. for $C_{23}H_{17}BrO_3S$: C, 60.94; H, 3.78; S, 7.07; Br, 17.62;
Found: C, 61.14; H, 3.93;, S, 6.94; Br, 17.79.

Preparation of Compounds of the Invention

Preparation Example A

Preparation of 6-methoxy-2-(4-methoxyphenyl)-3-(4-fluorobenzoyl)benzo[*b*]thiophene

[0069] To a slurry of 6-methoxy-2-(4-methoxyphenyl)-benzo[*b*]thiophene (1.02 g, 3.77 mmol) in dichloromethane (25 mL) at 5_C was added aluminum trichloride (0.600 g, 4.5 mmol). The slurry was observed to turn deep red. To this mixture was added p-fluorobenzoyl chloride (0.535 mL, 0.718 g, 4.52 mmol). The resulting mixture was stirred for 24 h at 5C, then quenched by addition of cold 1N HCl (20 mL) and partitioned between dichloromethane and 1N HCl. The aqueous layer was back extracted twice with dichloromethane, and the organics were washed with saturated aqueous NaCl and dried ($MgSO_4$). Following filtration and concentration, the residue was chromatographed on silica gel (8:1 hexanes:ethyl acetate) to afford 1.09 g (74%) of the title compound as a solid, mp = 108.1-109.0_C.

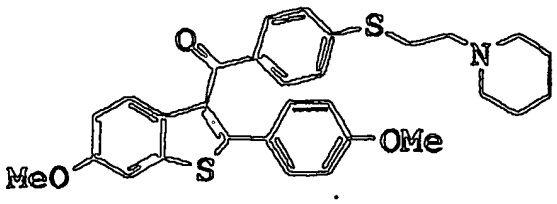
Infrared: (KBr) 2980, 2940, 2810, 1640, 1598, 1473, 1251, 1152, 831 cm^{-1};
^{1}H NMR ($CDCl_3$) δ 7.78 (dd, 2 H, *J* = 5.6, 8.7 Hz), 7.61 (d, 1 H, *J* = 8.9 Hz), 7.28 (m, 3 H), 6.98 (dd, 1 H, *J* = 2.5, 8.9 Hz), 6.94 (m, 3 H), 6.72 (d, 2 H, *J* = 8.7 Hz), 3.88 (s, 3 H), 3.73 (s, 3 H);
^{13}C NMR ($CDCl_3$) δ 192.8, 167.4, 164.0, 160.0, 157.9, 144.3, 140.2, 134.0, 133.9, 133.8, 132.7, 132.5, 130.6, 130.0, 125.8, 124.2, 115.7, 115.5, 115.1, 114.1, 104.6, 55.7, 55.3;

^{19}F NMR ($CDCl_3$) 8 48.31 (t, *J* = 6 Hz).
Elemental Analysis:
Calcd. for $C_{23}H_{17}FO_3S$: C, 70.39; H, 4.37; S, 8.17; F, 4.84.
Found: C, 70.21; H, 4.38; S, 8.27; F, 5.14.

Example 1

Preparation of 6-methoxy-2-(4-methoxyphenyl)-3-[4-(2-(piperidin-1-yl)ethylthio)benzoyl]benzo[*b*]thiophene

[0070]



Step a) Preparation of 2-(piperidin-1-yl)ethanethiol

[0071] Thiourea (6.0 g, 78.8 mmol) was stirred in anhydrous EtOH (25 ml) and 1-(2-chloroethyl) piperidine hydrochloride (14.2 g, 77.3 mmol) in anhydrous EtOH (50 ml) was added slowly over 20 min. via an addition funnel. The resulting solution was heated under reflux overnight. The ethanol was removed under reduced pressure. Ethanol (60 ml) was added followed by a solution of 77 mL of ethyl acetate and 20 mL of petroleum Ether. The product crystalized and was filtered. Some of this intermediate (4.36 g, 19.4 mmol) was dissolved in H_2O (10 ml) and NaOH(1.09g, 27.2 mmol) in H_2O (4.8 ml) was added. The mixture was heated with heat gun until a slight red oily layer could be detected. The organics were extracted with Et_2O, dried with $MgSO_4$, filtered. The ether layer contained the title product which was used without further purification.

Step b) Preparation of 6-methoxy-2-(4-methoxyphenyl)-3-[4-(2-(piperidin-1-yl)ethylthio)benzoyl]-benzo[*b*]thiophene

[0072] 2-(Piperidin-l-yl)ethanethiol (2.8g, 19.2 mmol, prepared as described in Step a) above) was stirred in 50 mL of diethyl ether under nitrogen at 0°C and NaH (0.676g of 60% dispersion in mineral oil) was added. The resulting solution was allowed to stir for 20 minutes. 6-Methoxy-2-(4-methoxyphenyl)-3-(4-fluorobenzoyl)benzo[*b*]thiophene (0.94g, 2.40 mmol, prepared as described in Preparation Example A above) in 100 mL of DMF was added. The reaction mixture was heated to reflux and stirred for 1 hour. The crude mixture was then poured into H20 and extracted three times with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (10% MeOH/$MeCl_2$) to afford 1.3g (98%) of the title compound.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, 2H, J = 8.5 Hz), 7.60 (d, 1H, J = 8.8 Hz), 7.34-7.24 (complex m, 5H), 6.69 (dd, 1H, J = 8.8, 2.2 Hz), 6.76 (d, 2H, *J* = 8.8 Hz), 3.90 (s, 3H), 3.76 (s, 3H), 3.56 (m, 4H), 3.01 (m, 2H), 2.58 (m, 2H), 2.29 (m, 2H), 1.88 (m, 3H), 1.43-1.34 (m, 1H).

FD+ MS for $C_{30}H_{32}NO_3S_2Cl$ = 517.

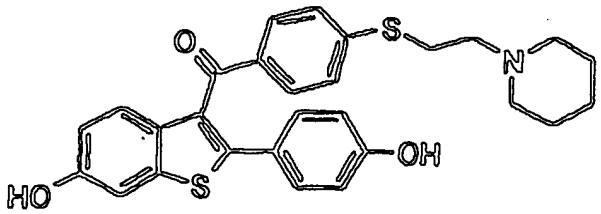
Elemental Analysis:

Calcd. for $C_{30}H_{32}NO_3S_2Cl$: C, 65.02; H, 5.82; N, 2.53; Found: C, 65.27; H, 6.01; N, 2.66.

Example 2

Preparation of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-(piperidin-1-yl)ethylthio)benzoyl]-benzo[*b*]thiophene

[0073]



[0074] 6-Methoxy-2-(4-methoxyphenyl)-3-[4-(2-(piperidin-1-yl)-ethylthio)benzoyl]benzo[*b*]thiophene (0.50g, 0.90 mmol, prepared as described in Step b) above) was dissolved in 10 mL of dichloromethane at 0°C and BBr_3 (3.6 ml of 1M, 3.6 mmol) was added. The resulting reaction mixture was stirred for 2 hours. The reaction mixture was then poured into H_2O and sufficient $NaHCO_3$ was added to keep pH between 7-9. It was extracted with ethyl acetate, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (10% MeOH/$MeCl_2$) to afford 0.13 g (29%) of the title compound.

^1H NMR (300 MHz, $CDCl_3$):	δ 7.69 (d, 1H, J = 8.8 Hz), 7.59 (d, 2H, J = 8.5 Hz), 7.29 (d, 1H, J = 2.2), 7.16 (d, 2H, J = 8.5 Hz), 7.11 (d, 2H, J - 8.8 Hz), 6.95 (dd, 1H, J = 8.8, 2.2 Hz), 6.58 (d, 2H, J = 8.8 Hz), 2.96 (br, 2H), 2.58 (m, 6H), 1.62 (br, 4H), 1.47 (br, 2H);
FD+ MS	for $C_{28}H_{27}NO_3S_2$ = 489;

Elemental Analysis:

Calcd. for $C_{28}H_{27}NO_3S_2$: C, 68.68; H, 5.56; N, 2.86;

Found: C, 68.86; H, 5.79; N, 2.88.

[0075] The compounds of formula I of the present invention are useful for alleviating the symptoms of hyperlipidemia, estrogen-dependent cancer, particularly estrogen-dependent breast and uterine carcinoma, and the conditions of osteoporosis, and cardiovascular diseases, particularly when the latter two conditions are associated with post-menapousal syndrome.

[0076] The terms "alleviating" or "treating" are defined to include prophylactic treatment of a person at risk of incurring one or more symptoms or pathological conditions listed above, holding in check such symptoms or pathological conditions, and treating existing symptoms or pathological conditions, as appropriate.

[0077] Compounds of the present invention are also effective for inhibiting uterine fibroid disease and endometriosis in women, and smooth muscle cell proliferation in humans. The following non-limiting biological test examples illustrate the methods of the present invention.

Biological Test Procedures

I. General Preparation for Post-Menopausal Rat Model

[0078] In the examples illustrating the methods, a post-menopausal model was used in which effects of different treatments upon various biological parameters were determined, including serum cholesterol concentration, uterine weight, estrogen receptor binding, uterine eosinophil peroxidase activity, MCF-7 cell proliferation, and bone density. Seventy-five day old female Sprague Dawley rats (weight range of 200 to 225 g) were obtained from Charles River Laboratories (Portage, MI). The animals were either bilaterally ovariectomized (OVX) or exposed to a sham surgical procedure (Intact) at Charles River Laboratories, and then shipped after one week. Upon arrival, they were housed in metal hanging cages in groups of 3 or 4 per cage and had ad libitum access to food (calcium content approximately 0.5%) and water for one week. Room temperature was maintained at 22.2° ± 1.7° C with a minimum relative humidity of 40%. The photoperiod in the room was 12 hours light and 12 hours dark.

II. Four Day Dosing Regimen

[0079] After a one week acclimation period (therefore, two weeks post-OVX), daily dosing with test compound was initiated. 17α-Ethynyl estradiol (EE_2) (Sigma Chemical Co., St. Louis, MO), an orally available form of estrogen, or the test compound were given orally, unless otherwise stated, as a suspension in 1% carboxymethyl cellulose or dissolved in 20% β-cyclodextrin. Animals were dosed daily for 4 days. Following the dosing regimen, animals were weighed and anesthetized with a ketamine:xylazine (2:1, v:v) mixture. A blood sample was collected by cardiac puncture. The animals were then sacrificed by asphyxiation with CO_2, the uterus was removed through a midline incision, and a wet uterine weight was determined.

A. Cholesterol Analysis

[0080] Blood samples were allowed to clot at room temperature for 2 hours, and serum was obtained following centrifugation for 10 minutes at 3000 rpm. Serum cholesterol was determined using a Boehringer Mannheim Diagnostics high performance cholesterol assay. Briefly the cholesterol was oxidized to cholest-4-en-3-one and hydrogen peroxide. The hydrogen peroxide was then reacted with phenol and 4-aminophenazone in the presence of peroxidase to produce a p-quinone imine dye, which was read spectrophotemetrically at 500 nm. Cholesterol concentration was then calculated against a standard curve. The entire assay was automated using a Biomek Automated Workstation.

B. Uterine Eosinophil Peroxidase (EPO) Assay

[0081] Uteri were kept at 4° C until time of enzymatic analysis. The uteri were then homogenized in 50 volumes of 50 mM Tris buffer (pH - 8.0) containing 0.005% Triton X-100. Upon addition of 0.01% hydrogen peroxide and 10 mM o-phenylenediamine (final concentrations) in Tris buffer, increase in absorbance was monitored for one minute at 450 nm. The presence of eosinophils in the uterus, as measured by assay of eosinophil peroxidase activity, is an indication of estrogenic activity of a compound. The maximal velocity of a 15 second interval was determined over the initial, linear portion of the reaction curve.

C. Results

[0082] Data presented in Table 1 below show comparative results among control ovariectomized rats, rats treated with EE_2, and rats treated with certain compounds of the present invention. Although EE_2 caused a decrease in serum cholesterol when orally administered at 0.1 mg/Kg/day, it also exerted a marked stimulatory action on the uterus so that the uterine weight of EE_2 treated rats was substantially greater than the uterine weight of ovariectomized test animals. This uterine response to estrogen is well recognized in the art.

[0083] In contrast, the compounds of the present invention substantially reduce serum cholesterol compared to the ovariectomized control animals without the general increase of uterine weight that is associated with estrogen compounds known in the art. This benefit of serum cholesterol reduction without adversely affecting uterine weight is quite rare and desirable.

[0084] As is expressed in the data below, estrogenicity also was assessed by evaluating the adverse response of eosinophil infiltration into the uterus. The compounds of the present invention did not cause an increase in the number of eosinophils observed in the stromal layer of ovariectomized rats, or in rare instances an increase only at the highest concentrations tested, as measured by assay of eosinophil peroxidase activity, while EE_2 caused a substantial, expected increase in eosinophil infiltration.

[0085] The data presented in Table 1 reflect the response of 5 or 6 rats per treatment.

Example	Dose (mg/kg PO)	Table 1 Uterine Weight (% inc. OVX)	Uterine EPO (Vmax)	Serum Cholesterol (% decrease OVX)
Ethynyl estradiol	0.1	144.1*	123.9*	80.3 *
2	0.1	3.5	3.3	-16.6
	1	23.1	1.2	37.5 *
	10	16.7	1.8	47.5*

* Indicates value is significantly different than OVX control.

[0086] In addition to the demonstrated benefits of the compounds of the present invention, especially when compared

to estradiol, the above data clearly demonstrate that these compounds are not estrogen mimetics. Furthermore, no deleterious toxicological effects (survival) were observed with treatment by any of the compounds of the present invention.

III. MCF-7 Proliferation Assay

[0087] MCF-7 breast adenocarcinoma cells (ATCC HTB 22) were maintained in MEM (minimal essential medium, phenol red-free, Sigma, St. Louis, MO) supplemented with 10% fetal bovine serum (FBS) (V/V), L-glutamine (2 mM), sodium pyruvate (1 mM), HEPES {(N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]10 mM), non-essential amino acids and bovine insulin (1 µg/ml) (maintenance medium). Ten days prior to assay, MCF-7 cells were switched to maintenance medium supplemented with 10% dextran coated charcoal stripped fetal bovine serum (DCC-FBS) assay medium) in place of 10% FBS to deplete internal stores of steroids. MCF-7 cells were removed from maintenance flasks using cell dissociation medium (Ca++/Mg++ free HBSS (phenol red-free) supplemented with 10 mM HEPES and 2 mM EDTA). Cells were washed twice with assay medium and adjusted to 80,000 cells/ml. Approximately 100 ml (8,000 cells) were added to flat-bottom microculture wells (Costar 3596) and incubated at 37° C in a 5% CO_2 humidified incubator for 48 hours to allow for cell adherence and equilibration after transfer. Serial dilutions of drugs or DMSO as a diluent control were prepared in assay medium and 50 ml transferred to triplicate microcultures followed by 50 ml assay medium for a final volume of 200 ml. After an additional 48 hours at 37° C in a 5% CO_2 humidified incubator, microcultures were pulsed with tritiated thymidine (1 uCi/well) for 4 hours. Cultures were terminated by freezing at -70° C for 24 hours followed by thawing and harvesting of microcultures. Samples were counted by liquid scintillation. Results in Table 2 below show the ED_{50} for certain compounds of the present invention.

Table 2

Compound	Y	R^1, R^2	ED_{50} (nM)
2	S	OH, OH	0.9

IV. MCF-7 Estrogen Receptor Binding Assay

[0088] Representative compounds of the present invention were tested in an estrogen receptor binding assay in which the test compounds were allowed to compete for binding with tritiated 17β-estradiol.

[0089] In the assay, serial dilutions of the test compound were mixed with 0.5 nM of ^{3}H-17β-estradiol, along with 0.5 mg/mL of protein from MCF-7 lysates, to a total volume of 0.14 mL. Binding was allowed to take place for 18 hours at 5_C, followed by the addition of 0.07 mL of dextran/charcoal and centrifugation to remove non-bound radioligand. Aliquots of supernate containing bound radioligand were mixed with scintillant and counted. Relative binding affinity (RBA) was calculated as:

$$RBA = \frac{IC_{50}\ 17b\text{-estradiol}}{IC_{50}\ test\ compound}$$

The data for representative compounds of the present invention are presented in Table 3.

Table 3

Example	Y	R^1, R^2	RBA*
2	S	OH, OH	0.15

*RBA = 1 for 17β-estradiol

Combination Therapy

[0090] The present invention also provides a method of alleviating post-menopausal syndrome in women which comprises the aforementioned method using compounds of the present invention and further comprises administering to a woman an effective amount of estrogen or progestin. These treatments are particularly useful for treating osteoporosis and lowering serum cholesterol because the patient will receive the benefits of each pharmaceutical agent while the compounds of the present invention would inhibit undesirable side-effects of estrogen and progestin. Activity of these combination treatments in any of the post-menopausal tests, *vide supra*, indicates that the combination treatments are useful for alleviating the symptoms of post-menopausal symptoms in women.

[0091] Various forms of estrogen and progestin are commercially available. Estrogen-based agents include, for example, ethenyl estrogen (0.01 - 0.03 mg/day), mestranol (0.05 - 0.15 mg/day), and conjugated estrogenic hormones such as Premarin® (Wyeth-Ayerst; 0.3 - 2.5 mg/day). Progestin-based agents include, for example, medroxyprogesterone such as Provera® (Upjohn; 2.5 -10 mg/day), norethylnodrel (1.0 - 10.0 mg/day), and nonethindrone (0.5 - 2.0 mg/day). A preferred estrogen-based compound is Premarin, and norethylnodrel and norethindrone are preferred progestin-based agents.

[0092] The method of administration of each estrogen- and progestin-based agent is consistent with that which is known in the art. For the majority of the methods of the present invention, compounds of the present invention are administered continuously, from 1 to 3 times daily. However, cyclical therapy may especially be useful in the treatment of endometriosis or may be used acutely during painful attacks of the disease. In the case of restenosis, therapy may be limited to short (1-6 months) intervals following medical procedures such as angioplasty.

[0093] As used herein, the term "effective amount" means an amount of compound of the present invention which is capable of alleviating the symptoms of the various pathological conditions herein described. The specific dose of a compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case including, for example, the compound administered, the route of administration, the state of being of the patient, and the pathological condition being treated. A typical daily dose will contain a nontoxic dosage level of from about 5 mg to about 600 mg/day of a compound of the present invention. Preferred daily doses generally will be from about 15 mg to about 80 mg/day.

[0094] The compounds of this invention can be administered by a variety of routes including oral, rectal, transdermal, subucutaneus, intravenous, intramuscular, and intranasal. These compounds preferably are formulated prior to administration, the selection of which will be decided by the attending physician. Thus, another aspect of the present invention is a pharmaceutical composition comprising an effective amount of a compound of the current invention, optionally containing an effective amount of estrogen or progestin, and a pharmaceutically acceptable carrier, diluent, or excipient.

[0095] The total active ingredients in such formulations comprises from 0.1% to 99.9% by weight of the formulation. By "pharmaceutically acceptable" it is meant the carrier, diluent, excipients, and salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

[0096] Pharmaceutical formulations of the present invention can be prepared by procedures known in the art using well known and readily available ingredients. For example, the compounds of the current invention, with or without an estrogen or progestin compound, can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl-pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

[0097] The compounds also can be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for example, by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular physiological location, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

[0098] Compounds of the present invention, alone or in combination with a pharmaceutical agent of the present invention, generally will be administered in a convenient formulation. The following formulation examples only are illustrative and are not intended to limit the scope of the present invention.

Formulations

[0099] In the formulations which follow, "active ingredient" means a compound of formula I.

Formulation 1: Gelatin Capsules

[0100] Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.1 - 1000

(continued)

Ingredient	Quantity (mg/capsule)
Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicone fluid 350 centistokes	0 - 15

[0101] The formulation above may be changed in compliance with the reasonable variations provided.

[0102] A tablet formulation is prepared using the ingredients below:

Formulation 2: Tablets

[0103]

Ingredient	Quantity (mg/tablet)
Active ingredient	2.5 - 1000
Cellulose, microcrystalline	200 - 650
Silicon dioxide, fumed	10 - 650
Stearate acid	5 - 15

The components are blended and compressed to form tablets.

[0104] Alternatively, tablets each containing 2.5 - 1000 mg of active ingredient are made up as follows:

Formulation 3: Tablets

[0105]

Ingredient	Quantity (mg/tablet)
Active ingredient	25 - 1000
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

[0106] The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

[0107] Suspensions each containing 0.1 - 1000 mg of medicament per 5 ml dose are made as follows:

Formulation 4: Suspensions

[0108]

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.1 - 1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 ml

(continued)

Ingredient	Quantity (mg/5 ml)
Flavor	q.v.
Color	q.v.
Purified water to	5 ml

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.
An aerosol solution is prepared containing the following ingredients:

Formulation 5: Aerosol

[0109]

Ingredient	Quantity (% by weight)
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00

[0110] The active ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to 30° C, and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remaining propellant. The valve units are then fitted to the container.
Suppositories are prepared as follows:

Formulation 6: Suppositories

[0111]

Ingredient	Quantity (mg/suppository)
Active ingredient	250
Saturated fatty acid glycerides	2,000

[0112] The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimal necessary heat. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.
An intravenous formulation is prepared as follows:

Formulation 7: Intravenous Solution

[0113]

Ingredient	Quantity
Active ingredient	50 mg
Isotonic saline	1,000 ml

[0114] The solution of the above ingredients is intravenously administered to a patient at a rate of about 1 ml per minute.

Formulation 8: Combination Capsule I

[0115]

Ingredient	Quantity (mg/capsule)
Active ingredient	50
Premarin	1
Avicel pH 101	50
Starch 1500	117.50
Silicon Oil	2
Tween 80	0.50
Cab-O-Sil	0.25

Formulation 9: Combination Capsule II

[0116]

Ingredient	Quantity (mg/capsule)
Active ingredient	50
Norethylnodrel	5
Avicel pH 101	82.50
Starch 1500	90
Silicon Oil	2
Tween 80	0.50

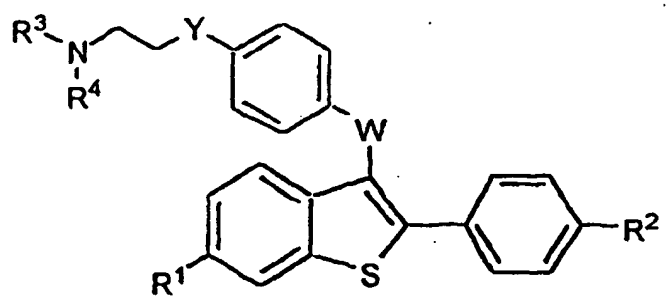
Formulation 10: Combination Tablet

[0117]

Ingredient	Quantity (mg/capsule)
Active ingredient	50
Premarin	1
Corn Starch NF	50
Povidone, K29-32	6
Avicel pH 101	41.50
Avicel pH 102	136.50
Crospovidone XL10	2.50
Magnesium Stearate	0.50
Cab-O-Sil	0.50

Claims

1. A compound having the formula:



or a pharmaceutically acceptable salt thereof wherein

R^1 and R^2 are independently selected from the group consisting of

hydroxy,

$-O(C_1-C_6$ alkyl),

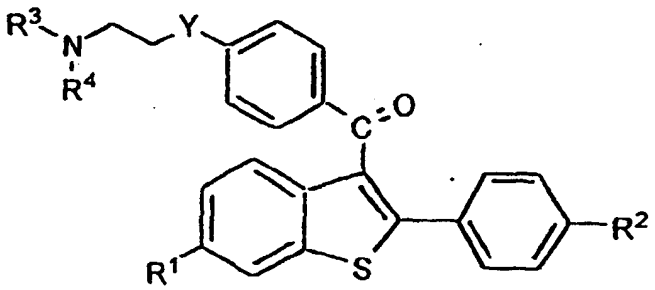
W is -CHOH-, -C(O)-, or $-CH_2-$;

Y is -S-; and

R^3 and R^4

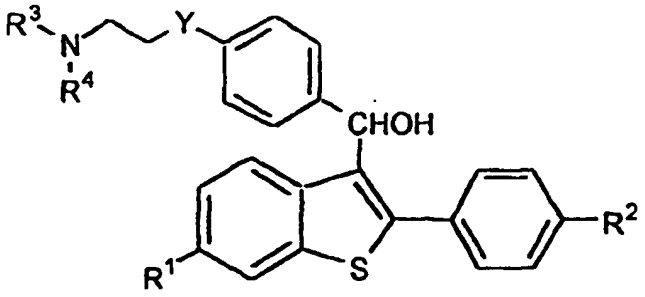
together with the nitrogen to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, or a 5- or 6-membered imide or cyclic amide ring.

2. A compound as defined by Claim 1 having the structure



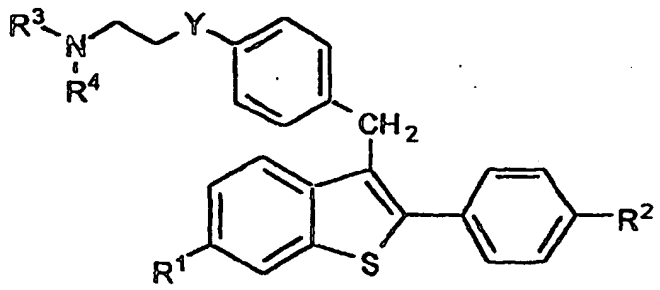
or a pharmaceutically acceptable salt thereof.

3. A compound as defined by Claim 1 having the structure



or a pharmaceutically acceptable salt thereof.

4. A compound as defined by Claim 1 having the structure



or a pharmaceutically acceptable salt thereof.

5. A compound as defined by Claim 1 wherein R^3 and R^4 combine, together with the nitrogen atom to which they are attached, to form a 1-pyrrolidinyl or 1-piperidinyl ring, or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1 wherein R^1 and R^2 are independently selected from -OH and $-OCH_3$.

7. A compound according to claim 6 selected from the group consisting of
6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-(piperidin-1-yl)-ethyithio)benzoyl]benzo *[b]* thiophene; and
6-methoxy-2-(4-methoxyphenyl)-3-[4-(2-(piperidin-1-yl)-ethylthio)benzoyl]benzo[*b]* thiophene; or a pharmaceutically acceptable salt thereof.

8. An intermediate useful in the preparation of a compound according to claim 1 selected from the group consisting of
6-methoxy-2-(4-methoxyphenyl)-3-(4-nitrobenzoyl)- benzo[b]thiophene;
6-methoxy-2-(4-methoxyphenyl)-3-(4-fluorobenzoyl)-benzo *[b]* thiophene; and
6-methoxy-2-(4-methoxyphenyl)-3-(4-bromobenzoyl)-benzo *[b]* thiophene.

9. A pharmaceutical composition comprising a therapeutically effective amount of compound as defined in any one of claims 1 - 7 in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

10. A pharmaceutical composition as defined by claim 9 further comprising a therapeutically effective amount of estrogen.

11. A pharmaceutical composition as defined by claim 9 further comprising a therapeutically effective amount of progestin.

12. A compound according to any one of claims 1 - 7 for use in medicine.

13. Use of a compound according to any one of claims 1 - 7 in the manufacture of a medicament for treating osteoporosis.

14. Use of a compound according to any one of claims 1 - 7 in the manufacture of a medicament for treating hyperlipidemia.

15. Use of a compound according to any one of claims 1 - 7 in the manufacture of a medicament for treating estrogen-dependent cancer.

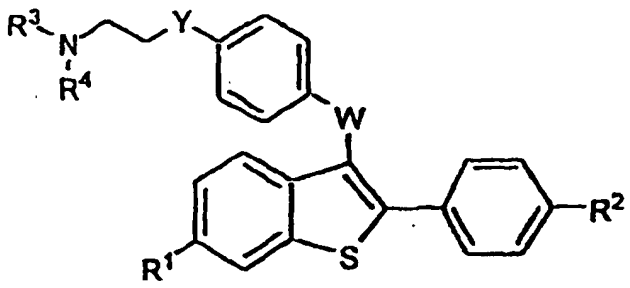
16. Use according to claim 15 wherein said estrogen-dependent cancer is breast cancer.

17. Use of a compound according to any one of claims 1 - 7 in the manufacture of a medicament for inhibiting aortal smooth muscle cell proliferation.

18. Use of a compound according to any one of claims 1 - 7 in the manufacture of a medicament for inhibiting restenosis.

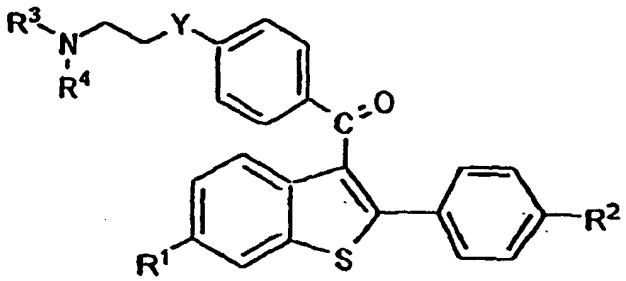
Patentansprüche

1. Verbindung der Formel



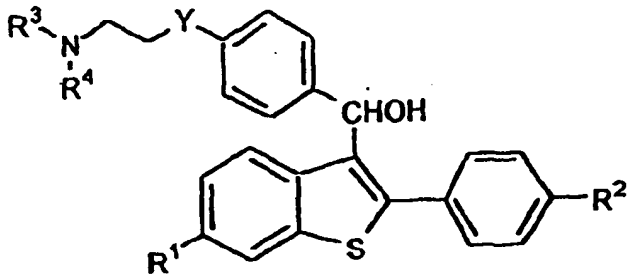
oder ein pharmazeutisch annehmbares Salz hiervon, worin
R^1 und R^2 unabhängig aus der Gruppe ausgewählt sind, die besteht aus Hydroxy und -O(C_1-C_6 Alkyl),
W für -CHOH-, -C(O)- oder -CH_2- steht,
Y für -S- steht und
R^3 und R^4 zusammen mit dem Stickstoff, an den sie gebunden sind, 1-Pyrrolidinyl, 1-Piperidinyl oder einen fünfoder sechsgliedrigen Imidring oder cyclischen Amidring bilden.

2. Verbindung nach Anspruch 1 mit der folgenden Struktur



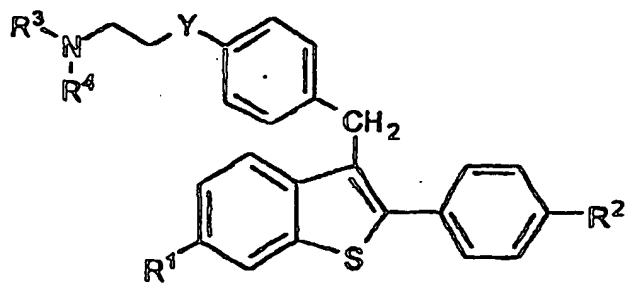
oder ein pharmazeutisch annehmbares Salz hiervon.

3. Verbindung nach Anspruch 1 mit der folgenden Struktur



oder ein pharmazeutisch annehmbares Salz hiervon.

4. Verbindung nach Anspruch 1 mit der folgenden Struktur



oder ein pharmazeutisch annehmbares Salz hiervon.

5. Verbindung nach Anspruch 1, worin R^3 und R^4 zusammen mit dem Stickstoffatom, an das sie gebunden sind, unter Bildung eines 1-Pyrrolidinyl- oder 1-Piperidinylrings kombinieren oder ein pharmazeutisch annehmbares Salz hiervon.

6. Verbindung nach Anspruch 1, worin R^1 und R^2 unabhängig ausgewählt sind aus -OH und $-OCH_3$.

7. Verbindung nach Anspruch 6, ausgewählt aus der Gruppe, die besteht aus
6-Hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-(piperidin-1-yl)ethylthio)benzoyl]benzo[b]thiophen und
6-Methoxy-2-(4-methoxyphenyl)-3-[4-(2-(piperidin-1-yl)ethylthio)benzoyl]benzo[b]thiophen oder ein pharmazeutisch annehmbares Salz hiervon.

8. Zwischenprodukt, das zur Herstellung einer Verbindung nach Anspruch 1 brauchbar ist, ausgewählt aus der Gruppe, die besteht aus
6-Methoxy-2-(4-methoxyphenyl)-3-(4-nitrobenzoyl)benzo[b]thiophen,
6-Methoxy-2-(4-methoxyphenyl)-3-(4-fluorbenzoyl)benzo[b]thiophen, und
6-Methoxy-2-(4-methoxyphenyl)-3-(4-brombenzoyl)benzo[b]thiophen.

9. Pharmazeutische Zusammensetzung, die eine therapeutisch wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 7 in Kombination mit einem pharmazeutisch annehmbaren Träger, Verdünnungsmittel oder Hilfsstoff enthält.

10. Pharmazeutische Zusammensetzung nach Anspruch 9, die ferner eine therapeutisch wirksame Menge an Östrogen enthält.

11. Pharmazeutische Zusammensetzung nach Anspruch 9, die ferner eine therapeutisch wirksame Menge an Progestin enthält.

12. Verbindung nach einem der Ansprüche 1 bis 7 zur Verwendung in der Medizin.

13. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 7 zur Herstellung eines Arzneimittels zur Behandlung der Osteoporose.

14. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 7 zur Herstellung eines Arzneimittels zur Behandlung der Hyperlipidämie.

15. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 7 zur Herstellung eines Arzneimittels zur Behandlung von Östrogen-abhängigem Krebs.

16. Verwendung nach Anspruch 15, worin der Östrogen-abhängige Krebs Brustkrebs ist.

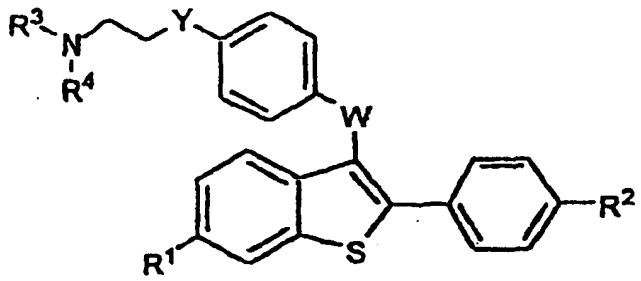
17. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 7 zur Herstellung eines Arzneimittels zur Hemmung der Proliferation der glatten Muskelzellen der Aorta.

18. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 7 zur Herstellung eines Arzneimittels zur Hemmung

der Restenose.

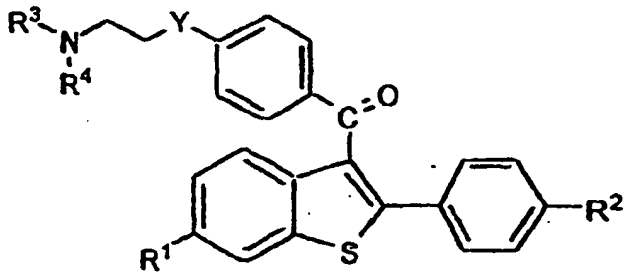
Revendications

1. Composé présentant la formule



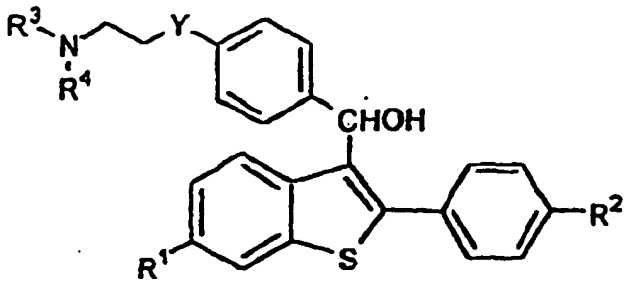
ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel
R^1 et R^2 sont choisis indépendamment dans le groupe constitué du groupe hydroxy, du groupe -O(alkyle en C_1 à C_6)
W représente un groupe -CHOH-, -C(O)- ou -CH_2-,
Y représente un groupe -S- et
R^3 et R^4 représentent ensemble avec l'atome d'azote auquel ils sont attachés un cycle 1-pyrrolidinyle, un cycle 1-pipéridinyle ou un cycle imide à cinq ou six membres ou un amide cyclique.

2. Composé tel que défini par la revendication 1 présentant la structure



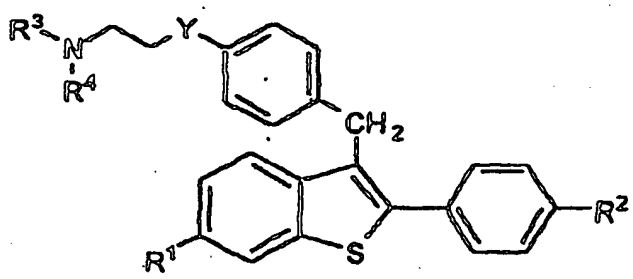
ou un sel pharmaceutiquement acceptable de celui-ci.

3. Composé tel que défini par la revendication 1, présentant la structure



ou un sel pharmaceutiquement acceptable de celui-ci.

4. Composé tel que défini par la revendication 1, présentant la structure



ou un sel pharmaceutiquement acceptable de celui-ci.

5. Composé tel que défini par la revendication 1, dans lequel R^3 et R^4 sont combinés avec l'atome d'azote auquel ils sont attachés pour former un cycle 1-pyrrolidinyle ou un cycle 1-pipéridinyle ou un sel pharmaceutiquement acceptable de celui-ci.

6. Composé selon la revendication 1, dans lequel R^1 et R^2 sont choisis indépendamment parmi le groupe -OH et le groupe $-OCH_3$.

7. Composé selon la revendication 6 choisi dans le groupe constitué du 6-hydroxy-2-(4-hydroxyphényl)-3-[4-(2-pipéridin-1-yl)-éthylthio)benzoyl]benzo[b]thiophène et du 6-méthoxy-2-(4-méthoxyphényl)-3-[4-(2-pipéridin-1-yl)-éthylthio)benzoyl]benzo[b]thiophène ou un sel pharmaceutiquement acceptable de celui-ci.

8. Intermédiaire utile dans la préparation d'un composé selon la revendication 1, choisi parmi le groupe constitué du 6-méthoxy-2-(4-méthoxyphényl)-3-(4-nitrobenzoyl)benzo[b]thiophène, du 6-méthoxy-2-(4-méthoxyphényl)-3-(4-fluorobenzoyl)benzo[b]thiophène et du 6-méthoxy-2-(4-méthoxyphényl)-3-(4-bromobenzoyl)benzo[b]thiophène.

9. Composition pharmaceutique comprenant une quantité thérapeutiquement efficace d'un composé tel que défini dans l'une quelconque des revendications 1 à 7 en association avec un support, un diluant ou un excipient pharmaceutiquement acceptable.

10. Composition pharmaceutique telle que définie dans la revendication 9, comprenant en outre une quantité thérapeutiquement efficace d'estrogène.

11. Composition pharmaceutique telle que définie dans la revendication 9, comprenant en outre une quantité thérapeutiquement efficace de progestérone.

12. Composé selon l'une quelconque des revendications 1 à 7 pour une utilisation dans le domaine médical.

13. Utilisation d'un composé selon l'une quelconque des revendications 1 à 7 dans la préparation d'un médicament pour le traitement de l'ostéoporose.

14. Utilisation d'un composé selon l'une quelconque des revendications 1 à 7 dans la préparation d'un médicament pour le traitement de l'hyperlipidémie.

15. Utilisation d'un composé selon l'une quelconque des revendications 1 à 7 dans la préparation d'un médicament pour le traitement d'un cancer dépendant oestrogéno-dépendant.

16. Utilisation selon la revendication 15, dans laquelle ledit cancer oestrogéno-dépendant est le cancer du sein.

17. Utilisation d'un composé selon l'une quelconque des revendications 1 à 7 dans la préparation d'un médicament

pour inhiber la prolifération des cellules du muscle lisse de l'aorte.

18. Utilisation d'un composé selon l'une quelconque des revendications 1 à 7 dans la préparation d'un médicament pour inhiber la resténose.